



CASE REPORT

Bullous dermatosis associated with gemcitabine therapy for non-small-cell lung carcinoma

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KEYWORDS

Gemcitabine;
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Summary Gemcitabine considered is to be a well-tolerated cytostatic drug with little known side effects. Cutaneous reactions are well known but still rarely reported.

We report the case of a 75-year-old man with stage IV non-small-cell lung carcinoma treated with combination of gemcitabine 1000 mg/m² and cisplatin 75 mg/m² repeated every 28 days, who developed bilateral cutaneous bullous lesions of lower limbs following gemcitabine administration. Histopathologic examination did not show any toxidermy aspect and there was not any sign of immunoglobulin deposit in direct immunofluorescence test. Chemotherapy was stopped and lesions disappeared without any treatment. Even delayed with regard to gemcitabine administration, the causal relationship of gemcitabine treatment with skin reaction is possible according to the Naranjo probability scale. Pathologists should be aware of this kind of side effect in managing chemotherapy drugs and report any dermatologic reactions in order to identify the cause of toxicity and avoid a misdiagnosis.

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Introduction

Gemcitabine is the hydrochloride salt of a deoxycytidine analogue, with demonstrated antineoplastic activity against solid tumours and thus against

non-small-cell lung cancer, when used either alone or in combination with platinum compounds.^{1–3}

Gemcitabine has a relative lack of side effects, including nausea, emesis, myelosuppression, peripheral oedema and pulmonary toxicity.^{1,4}

Previous reports have shown that gemcitabine had little cutaneous toxicities, such as alopecia and maculopapular rash.⁵ Nevertheless, other kinds of skin adverse effects still being sparsely reported.

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We report a case of gemcitabine-related skin reaction and discuss the causal relationship.

Case report

A 75-year-old man was diagnosed as having stage IV non-small-cell lung carcinoma with suparenal metastasis. Palliative chemotherapy with intravenous gemcitabine 1000 mg/m² on days 1, 8 and 15 coupled with intravenous cisplatin on day 15, repeated every 28 days was begun in September 2003. The two first cycles were conducted without incidents.

On day 8 of the third cycle and before gemcitabine administration, the patient presented cough with peripheral legs oedema. The drug administration was delayed. When hospitalised 4 days after, physical examination of the patient revealed bilateral oedema of lower legs with 3 cm diameter bubble of the anterior face of right lower leg and numerous little bubbles of the left one (Fig. 1). A skin biopsy specimen taken from the bullous lesion completed with direct immunofluorescence study showed no toxidermy aspect with no sign of fluorescence with immunoglobulin G (IgG), IgA or IgM. To explore legs oedema aetiology, the laboratories studies revealed normal serum kidney parameters (urea = 2.52 mmol/l, creatinine = 65.2 µmol/l, creatinine clearance = 93.3 ml/min when measured with cockcroft and Gault method)

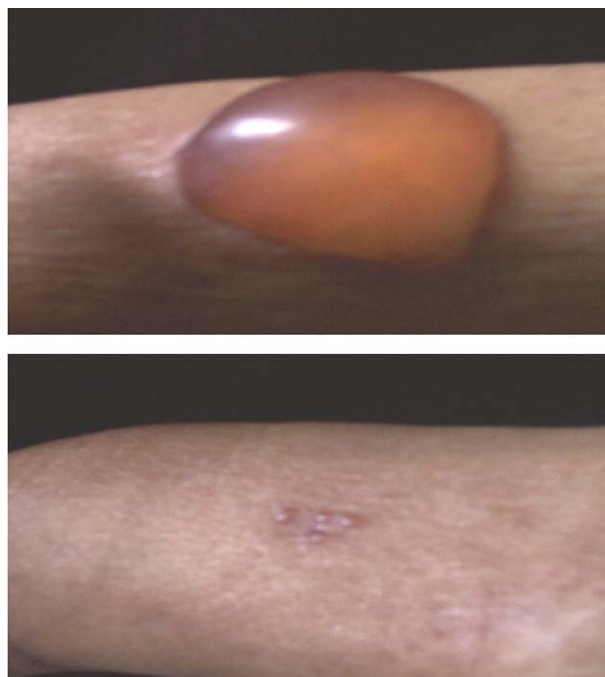


Figure 1 Skin bullous of right leg above and left leg below.

and normal serum liver enzymes (aspartate aminotransferase = 25.5 UI/l, alanine aminotransferase = 8.5 UI/l and INR = 1); cardiac echography was also normal.

An abdominal and pelvic echography showed no abnormalities others than metastatic suparenal localisation.

Inquire of pharmacological imputability showed no causal relationship between gemcitabine and skin reaction because of delayed time of lesions appearance of 12 days.

Skin lesions disappeared without specific treatment, and during follow-up, the patient died because of the progression of the disease.

Discussion

There is some hypothesis that could explain skin lesions occurrence during chemotherapeutic agents' administration in cancer patients, e.g. cutaneous metastasis from the primary cancer, paraneoplastic syndrome or a drug reaction.⁶

In the described patient, a drug skin reaction seems most probable since histopathologic examination is normal. The accused drugs are gemcitabine and cisplatin.

Gemcitabine is generally a well-tolerated cytostatic and its most frequent cutaneous side effects are well documented, including alopecia, maculopapular eruption and are reported with a prevalence of 25.7–39%.¹ Whereas, few other adverse effects are less common and rarely reported; these include pseudolymphoma,² lipodermatosclerosis reaction,¹ linear IgA bullous dermatosis (LABD),⁷ limbs acronecrosis,⁸ erysipeloid rash developed in lymphedema areas or following radiotherapy^{9,10} and scleroderma-like reaction.¹¹ More severe drug-induced reactions with gemcitabine, such as toxic epidermal necrolysis and Stevens–Johnson syndrome, were reported during concurrent chemotherapy and radiotherapy.^{12,13}

We describe a further patient showing a cutaneous bullous lesions some days following gemcitabine therapy. This bullous dermatosis is not common and has been described in 1/1000–10,000 of cases treated with chemotherapy. Also, there are neither histological findings of toxidermy nor direct immunofluorescence deposit, and gemcitabine can be involved in this side effect; in fact, although the half-life of elimination of gemcitabine ranges from 11 to 26 min and that of its metabolites is from 0.7 to 12 h, Naranjo probability scale¹⁴ showed that the causal relationship of gemcitabine treatment with cutaneous eruption is possible (calculated scale = 4).

We tried to explain the pathogenesis of bullous occurrence; in fact, gemcitabine is usually excreted renally, its pharmacokinetics might be altered by legs oedema, inactivation is so slower and drug might accumulate in the subcutaneous and cutaneous tissue, increasing local toxicity. This explanation had been previously reported with erysipeloid rash occurring in lymphedema areas.⁹

Some almost identical cases were reported with LABD induced by gemcitabine⁷; in fact, this lesion is an autoimmune, subepidermal, vesicubullous disease that has been commonly associated with vancomycin therapy, appearing 24 h to 15 days after the first drug dose and also rarely with gemcitabine.^{7,15} In the case reported, lesions aspects are similar to LABD, but the difference is the lack of immunofluorescence positivity.

Peripheral oedema occurs in up to 20% of patients treated with gemcitabine; the oedema is typically mild, requiring discontinuation of the drug in less than 1% of patients. Most patients require no therapy. However, in cases of peripheral oedema of grade II or higher, suspension of gemcitabine and treatment with corticosteroids are often necessary, and permanent discontinuation of gemcitabine may be required on occasion.¹⁶

In our patient, no other causes of peripheral oedema were found and thus, this had been associated with gemcitabine therapy.

Incrimination of cisplatin also seems to be unlikely as time course between the last cisplatin administration and skin reaction of 45 days is so long to make it the causative agent. Moreover, calculated Naranjo score is equal to zero and thus, the causative relationship is doubtful.

Gemcitabine appears more likely involved in this skin reaction and pathologists should be aware about any skin reactions during chemotherapeutic agents administration in order to identify the cause of toxicity and avoid misdiagnosis.

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